Annex II

Scientific conclusions and grounds for lifting of the suspension and amendment of the marketing authorisations for aprotinin containing medicinal products presented by the EMA

Scientific conclusions

Overall summary of the scientific evaluation of referral on antifibrinolytics **Aprotinin containing medicinal products** (see Annex I)

Antifibrinolytics (e.g. aprotinin, aminocaproic acid and tranexamic acid), are a class of haemostatic agents used to prevent excessive blood loss. Aprotinin, a naturally occurring polypeptide, is an inhibitor of proteolytic enzymes. It has a broad action on proteolytic enzymes such as plasmin, trypsin, and kallikrein. The lysine analogues epsilon aminocaproic acid (EACA, also referred as aminocaproic acid) and tranexamic acid (TXA) inhibit more specifically the conversion of plasminogen to plasmin.

In March 2010 Germany triggered an article 31 referral to assess the benefits and risks of the antifibrinolytic drugs aprotinin, EACA and TXA in all their approved indications. The marketing authorisations for aprotinin were suspended when concerns over its safety were raised in a previous review in 2007. The preliminary results of a randomised controlled clinical trial, the 'Blood conservation using antifibrinolytics: a randomised trial in a cardiac surgery population' (BART) study, had shown that although the use of aprotinin was associated with less serious bleeding than either of the comparator drugs, an increase in 30 day all-cause mortality had been observed among patients receiving aprotinin compared to patients taking other medicines. These concerns echoed those of a few published observational studies. The marketing authorisations of EACA and TXA were not affected by the initial 2007 review.

Several data sources informed the opinion of the Committee, including available data from clinical studies, published literature, spontaneous reports and other data submitted by marketing authorisation holders (MAHs) of medicinal products containing aprotinin, EACA or TXA. A CHMP scientific advisory group (SAG) meeting was held in October 2011 and its views were considered by the CHMP in the framework of this review.

Separate opinions and conclusions were issued by the CHMP for the three antifibrinolytics (aprotinin, EACA and TXA). This document presents the conclusions on aprotinin.

Aprotinin

The marketing authorisations for aprotinin were suspended following the preliminary results of the BART study in 2007, and concerns raised over some observational studies.
The final results of BART study have since become available, together with important new analysis of the study data. A comprehensive review was undertaken and the CHMP concluded that the final BART study results were seriously compromised by several newly identified major methodological deficiencies, which were considered crucial to the validity and interpretation of the results. The deficiencies included the unexplained exclusion of patients from analysis, underlying differences in baseline characteristics between the study groups which were not homogenous in spite of randomisation, and the apparent reduced level of heparinisation in the aprotinin arm which would increase the risk of thrombogenic events in this group.

Based on the final results and new evidence from re-analysis of data pointing out the deficiencies of the study that emerged after finalisation of the BART study, the CHMP is of the opinion that these data are not reliable and cannot be considered with regards to the cardiovascular risks of aprotinin. Overall, the CHMP considered that the BART study was not designed to reliably determine the risk of death associated with aprotinin in relation to EACA or TXA and the results of higher mortality initially observed in aprotinin treated patients may be due to chance. The CHMP noted that since the initial review in 2007, more data has become available, in particular the final study results, and more importantly new analysis of the BART study. These new data have now made it possible to identify the major flaws of the BART study, not identifiable before.

The CHMP noted that the findings from other randomised clinical trials and meta-analysis of randomised clinical trials (when the BART study is excluded) do not provide evidence of an association between aprotinin and perioperative mortality.

In the initial review in 2007 concerns had also been raised by the findings of three observational studies. The results of re-analysis of two of these studies did not show a statistically significant association between aprotinin treatment and myocardial infarction, and other cardiovascular endpoints; methodological questions were raised over a third observational study where a supplementary analysis also did not show a significant association between aprotinin and seven-day in-hospital mortality. New

observational studies are now available and results showed that aprotinin did not affect in-hospital mortality, with one study reporting a statistically significant mortality 'benefit' for aprotinin in high-risk cardiac surgery patients, compared with TXA. The CHMP noted the uncertainties and advised that the interpretation of all available data from observational studies is limited.
The CHMP considered that the efficacy of aprotinin has been clearly demonstrated in prospective randomised trials and meta-analysis of clinical trials which show that aprotinin reduces the incidence of massive bleeding, reduces the need for transfusion of blood products and reduces the need for re-surgery for bleeding in patients undergoing cardiac surgery requiring cardiopulmonary bypass (CPB).

Aprotinin was already indicated for prophylactic use to reduce perioperative blood loss and the need for blood transfusion in those patients undergoing CPB in the course of CABG who were at an increased risk for blood loss and blood transfusion. Sufficient evidence of efficacy in this patient population is available. The new data available to date however showed that the indication, and other sections of the product information, merited change, to take due account of known risks and the uncertainties associated with such risks. The product has been used outside its indication, with several trials where risks were observed conducted in a wider patient population. The CHMP considered that a clarification should be included in the wording of the indication to reflect that the product should be used in patients undergoing CPB in the course of 'isolated CABG' surgery, as efficacy and safety of aprotinin in more extensive surgery has not been sufficiently characterised. In addition, aprotinin should be used only in adult patients (data in children are not available) who are at 'high-risk' of major blood loss. There are no indications that the efficacy would vary by age or that the safety pattern of aprotinin would be different in elderly patients as compared to the overall study populations.

A review of the product information was undertaken to specify the agreed target population and update the clinical part of the product information to ensure that the information to healthcare professionals and patients is up to date. The quality review of documents templates were taken into account during this review.

The CHMP considered that overall the data provided illustrate the risks associated with inadequate monitoring of the anticoagulative effect of heparin administered in the CABG procedure. Other notable safety concerns include the identified risk for transient renal impairment, which is a well characterised unfavourable effect of treatment with aprotinin. This is important to take into consideration when treating patients with known pre-existing impairment and in patients concomitantly treated with drugs that may affect renal function. Anaphylactic reactions are another well-known adverse effect that primarily occurs after repeated treatment. In case of repeated treatment, physicians should be aware of the risk, and manage their patients adequately. The CHMP considered that all of these risks, along with the uncertainties on the findings from clinical trials and observational studies on mortality, should be appropriately reflected through warnings and recommendations in the product information and captured in the risk management plan.

All risks of aprotinin known to date were considered. There is no evidence of an association between aprotinin and perioperative mortality from randomised clinical trials when the BART study is excluded. The observational studies have provided conflicting results related to mortality as discussed above. Reduction in massive bleeding, transfusion need and risk for re-surgery due to bleeding are considered meaningful clinically important effects of aprotinin, and when considering the overall data on the known risks, the CHMP considered that the balance is clearly positive in the identified patient population. Re-surgery due to bleeding carries high risk for increased morbidity which also was emphasised by the group of external experts consulted by the CHMP. The reduction of the need for re-surgery after coronary artery bypass grafting (CABG) demonstrated for aprotinin is considered to be a benefit of high clinical relevance. Therefore, taking the totality of data into account it is judged that the previous signal for an increased mortality associated with the use of aprotinin is refuted provided that aprotinin is given in the identified target population and the recommendations for its use are followed. In this regard, a study on the profile of aprotinin use is needed, particularly in light of the importance of adequate anticoagulation. The CHMP considered that a registry should be conducted by MAHs of aprotinin containing medicinal products affected by this review. The registry, which will be mandatory for use of the product, will monitor the pattern of use in participating countries and record utilisation information. The number of patients who receive aprotinin, indication for administration, patient characteristics and risk factors and conditions of use including data on heparinisation of patients treated with aprotinin are some of the information to be collected. The MAHs will submit a revised protocol for the registry to national competent authorities.

Taking into account all the data available on the efficacy and safety of aprotinin to date, the CHMP considered that there is clear evidence of a patient population in which the efficacy of systemic aprotinin clearly outweighs its risks. The proposed indication is for prophylactic use to reduce blood

loss and blood transfusion in adult patients who are at high risk of major blood loss undergoing isolated cardiopulmonary bypass graft surgery (i.e. coronary artery bypass graft surgery that is not combined with other cardiovascular surgery).

As a result, the Committee agreed on the lifting of the suspension for aprotinin with the balance of risks and benefits considered positive in the following revised indication for aprotinin:

Aprotinin is indicated for prophylactic use to reduce blood loss and blood transfusion in adult patients who are at high risk of major blood loss undergoing isolated cardiopulmonary bypass graft surgery (i.e. coronary artery bypass graft surgery that is not combined with other cardiovascular surgery).

Aprotinin should only be used after careful consideration of the benefits and risks, and the consideration that alternative treatments are available (see section 4.4 and 5.1).

Divergent positions are appended to the Opinion.

A direct healthcare professional communication (DHPC) was agreed to provide prescribers with information on the review and an update on the safety information for aprotinin.

Grounds for lifting of the suspension and amendment of the marketing authorisations of aprotinin containing medicinal products listed in Annex I

Whereas

- The Committee considered the procedure under Article 31 of Directive 2001/83/EC, for aprotinin, aminocaproic acid and tranexamic acid (see Annex I).

- The Committee considered all data provided by the MAHs in writing and at the oral explanation, including data available from literature reviews and the outcome of a scientific advisory group.

- The Committee concluded that evidence from randomised clinical trials and observational studies support the use of aprotinin in reducing the incidence of massive bleeding, the need for transfusion of blood products and the need for re-surgery for bleeding.

- The CHMP concluded that the BART data and the signal on increased mortality associated with aprotinin compared to EACA and TXA were not considered reliable, based on the totality of evidence now available since the review of aprotinin undertaken in 2007, including more recent observational studies, the new analyses of the BART study data and the identified major study flaws, and taking the advice of the SAG into account. The CHMP noted that since the initial review in 2007, more data has become available, such as new observational studies, the final study results of the BART study, and more importantly new analyses of the BART study. These new data have now made it possible to identify the major flaws of the BART study, not identifiable before.

- The Committee considered that the available randomised clinical trial and meta-analysis of clinical trials (when the BART study is excluded) do not give evidence of an association between aprotinin and perioperative mortality. No firm conclusion on cardiovascular risks can be made on the BART study due to several serious methodological issues identified. In addition, results from observational studies are conflicting. Taking the totality of data into account it is judged that the previous signal for an increased mortality associated with the use of aprotinin should be refuted provided that the drug is given in the identified target population of adult patients at high risk of major blood loss undergoing isolated coronary artery bypass graft (CABG) surgery and the recommendations for its use are followed.

- The Committee considered that the product information should be updated to ensure that the information to healthcare professionals and patients is up-to-date. Recommendations on adequate monitoring of the anticoagulative effect of heparin administered in the CABG procedure should be reflected in the product information. Special attention is also to be given to patients with renal impairment and to the possible occurrence anaphylactic reactions. All risks should be captured in the risk management plan. In addition, a registry must be conducted by MAHs of aprotinin containing medicinal products in order to gather more information on the profile of aprotinin use. A restricted distribution of aprotinin is envisaged with aprotinin available only to centres that perform cardiac surgery on cardio-pulmonary bypass and that commit to participate in the registry.

Therefore the CHMP concluded that the balance of risks and benefits for aprotinin is positive under normal conditions of use subject to the revision of the indication as follows:

prophylactic use to reduce blood loss and blood transfusion in adult patients who are at high risk of major blood loss undergoing isolated cardiopulmonary bypass graft surgery (i.e. coronary artery bypass graft surgery that is not combined with other cardiovascular surgery).
Aprotinin should only be used after careful consideration of the benefits and risks, and the consideration that alternative treatments are available (see section 4.4 and 5.1).

On the basis of the above, the Committee recommended the lifting of the suspension and the amendment of the marketing authorisations for the medicinal products containing aprotinin referred to in Annex I for which the amendments to the product information are set out in annex III of the opinion.

The scientific conclusions and the grounds for the lifting of the suspension and amendment of the marketing authorisation are set out in annex II of the opinion.

The conditions with regard to the safe and effective use of the medicinal product to be implemented by the member states are set out in annex IV of the opinion.